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***o*-Benzenedisulfonimide as a Reusable Acid Catalyst for an Easy, Efficient and Green Synthesis of Tetrahydroisoquinolines and Tetrahydro- β -carboline through Pictet-Spengler Reaction.**

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Abstract

The synthesis of tetrahydroisoquinolines and tetrahydro- β -carboline, using the Pictet-Spengler reaction, was carried out in the presence of a catalytic amount of *o*-benzenedisulfonimide, which worked as a Brønsted acid organocatalyst. The reaction conditions were mild and green and good target product yields were achieved. The catalyst was easily recovered and purified, ready to be used in further reactions with economic and ecological advantages.

Keywords: homogeneous catalysis; tetrahydroisoquinoline; tetrahydro- β -carboline; Brønsted acid; 2-arylethanamines.

The Pictet-Spengler reaction^{1a-d} is an useful and important synthetic protocol for the preparation of tetrahydroisoquinoline^{1e} and tetrahydro- β -carboline ring systems.^{1f} These are present in numerous natural and synthetic organic compounds and possess various biological activities. For instance, tetrahydroisoquinolines show powerful anti-tumor, antimicrobial, anti-HIV activities;^{1g-h} tetrahydro- β -carbolines are interesting hypnotic, anxiolytic, antimicrobial, antiviral, anti-tumor and anti-convulsant compounds.¹ⁱ

Usually, Brønsted acids (recent examples are: H⁺ montmorillonite,² trifluoroacetic acid,^{1g,3} carboxylic acids-thiourea,⁴ *p*-toluensulphonic acid,⁵ perfluorooctanesulphonic acid in water,⁶ chiral phosphoric acids⁷) or Lewis acids (recent examples are: calcium complexes,⁸ Yb(OTf)₃,⁹ AuCl₃/AgOTf¹⁰) are employed as catalysts to promote this reaction, involving the cyclization of iminium ions (or imines) resulting from the dehydration reaction of 2-arylethylamine derivatives with aldehydes.

We have recently reported the use of *o*-benzenedisulfonimide (**1**, Figure 1) in catalytic amounts as a safe, non-volatile and non-corrosive Brønsted acid in some acid-catalyzed organic reactions such as etherification,^{11,12} esterification,^{11,12,13} acetalization,^{11,12} the Ritter reaction,¹⁴ Nazarov electrocyclization,¹⁵ disproportionation of dialkyl diarylmethyl ethers,¹⁶ Hosomi-Sakurai reaction¹⁷ and Friedlander annulation¹⁸.

Figure 1: *o*-benzenedisulfonimide 1

In general, all synthetic methods were performed under mild reaction conditions and showed short reaction times, good selectivity and the absence or minimal formation of by-products. Moreover, it is worthwhile highlighting another advantage of all the above reactions: **1** can be easily and almost completely recovered from the reaction mixtures in high yield, due to its complete solubility in water. This permits its reuse in other reactions, immediately or after a fast purification step on a cation-exchange resin without any loss of catalytic activity, with economic and ecological advantages.

In this letter we wish to propose a simple, efficient and green synthesis of tetrahydroisoquinolines and tetrahydro- β -carbolines under the Pictet-Spengler protocol in the presence of **1** which acts as a reusable Brønsted acid catalyst (Scheme 1 and 2).

Scheme 1: Synthesis of tetrahydroisoquinolines **5**

Firstly, various aromatic and heteroaromatic aldehydes **3a,3c-g** were reacted with 2-(3,4-dimethoxyphenyl)ethanamine (**2a**); the reaction mixture was heated at 80°C, in the presence of 10 mol% of **1** and in the absence of a solvent. The reaction times were between 6 and 12 hours. As shown in Table 1 (entries 1, 5-9), the target tetrahydroisoquinolines **5a,5e-i** were always obtained in excellent yields, more than 80%. These high yields are independent of the type and position of the substituents. The work-up was very simple: it was sufficient to add water to the crude residue, filter and wash the resulting solid with additional water on a Buchner funnel.¹⁹

Table 1: Synthesis of tetrahydroisoquinolines **5**

Furthermore, **1** was recovered in excellent yields (for example: Table 2, entry 1, 89 %), by simply evaporating the aqueous washings under reduced pressure.¹⁹ Recovered **1** was reused as a catalyst in other two consecutive reactions between **2a** and **3a**. The results are listed in Table 2. The reaction time increased after each run, but the yields of **5a** and the recovery yield of **1** were always fairly good

Table 2: Consecutive reactions with **1**

Using acetophenone (**3b**) as a carbonyl partner, we also obtained good results (Table 1, entry 4). Using the less reactive 2-(3-methoxyphenyl)ethanamine (**2b**), the yield of **5b** was lower and the reaction time was longer (24 hours, Table 1, entry 2). Reacting 2-phenylethanamine (**2c**), no traces of **5c** were detected; only the intermediate *N*-benzyliden-2-phenylethyl amine (**4c**) formed. This intermediate cannot cycle due to the lack of electron donating groups on the aromatic ring (Table 1, entry 3).

To further explore the synthetic usefulness of **1** in Pictet-Spengler reactions we reacted tryptamine **6** with aromatic aldehydes **3a**, **3c-g** in order to obtain tetrahydro- β -carboline **8** (Scheme 2).

Scheme 2: Synthesis of tetrahydro- β -carboline **8**

These reactions needed 20% mol of **1**, reactions time between 8 and 16 hours and heating to 80°C; however the yields of **8** and the recovery yield of **1** were always good (Table 3, entries 1-6). It was always possible to recover **1** in good yields (for example: Table 3 entry 1, 85%).

Table 3: Synthesis of tetrahydro-β-carbolines **8**

It is worth noting that the Pictet-Spengler reactions, performed with other Brønsted acids as catalysts, usually require the presence of a solvent, either during the reaction or the work-up^{3,4,5,7,8,9,10} or harsher reaction conditions.^{4,5,8,10}

We then examined the extension of this procedure to aliphatic aldehydes. However, the reaction of **2a** with primary aldehyde **3h** gave a small amount of product **16a**, which arises from homo-aldol condensation and imine formation (Table 1, entry 10; Scheme 3) as well as the target product **5j**.⁷ The amount of **16b** significantly increased when **2b** was reacted with **3h** (Table 1, entry 11). Furthermore, the reactions of **6** with **3h** furnished only **16c** (Table 3, entry 7).

The mechanism of the Pictet-Spengler reaction, described in Scheme 3, implies the formation of the iminium salt **11**, its cyclization and subsequent deprotonation to give the final product **12**.

Scheme 3: Mechanism of Pictet-Spengler reaction

However, when tautomerism between imine **13** and amine **14** is possible (probably favoured by **1**; Scheme 3), **14** can react with a protonated aldehyde initially furnishing intermediate **15** and then the product of the homo-aldol condensation **16**.⁷ Since the cyclization reaction is greatly facilitated by the presence of electron donating groups on the aromatic ring, we could suppose that in the presence of two methoxy groups the rate of the cyclization reaction is greater than the rate with which **13** can tautomerize. In the presence of only one methoxy group however, since the rate of cyclization decreases, the possibility of tautomerism between **13** and **14** increases and accordingly increases the yield of **16**. On the other hand, when the indolyl ring is present, tautomerization is faster than cyclization and the only product was **16**. To further the examination of aliphatic aldehydes, it is worth noting that the reactions of **2a** with **3i-k**, under the same conditions as described above for aromatic aldehydes, provided excellent yields of **5l-n** (Table 1, entries 12-14). The greater steric hindrance of aldehydes **3i** and **3j** probably made their electrophilic attack on **14** more difficult, therefore cyclization was favored. On the other hand, only **16d** was formed and no traces of **8h** were detected when **6** was reacted with **3i** (Table 3, entry 8). The reaction between **6** and **3j** also failed (Table 3, entry 9). Obviously, the only positive result was obtained by reacting **6** with tertiary aldehyde **3k** (Table 3, entry 10).

In conclusion, we have proposed a mild, easy, efficient and green method for the synthesis of tetrahydroisoquinoline and tetrahydro- β -carboline through the Pictet-Spengler reaction in the presence of *o*-benzenedisulfonimide (**1**) used as a reusable homogeneous catalyst. The advantages of performing the Pictet-Spengler reaction in the presence of **1** as a catalyst can be summarized as follows: 1) the use of a safe, non-volatile, non-corrosive Brønsted acid, 2) good recovery yields of **1** at the end of the reactions by simply evaporating aqueous washings, 3) the target products are obtained generally in excellent yields

4) the reactions are carried out under easy, mild and green conditions with economic and ecological benefits.

Acknowledgments

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19. 6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**5a**): representative procedure for the preparation of tetrahydroisoquinolines **5**: o-Benzenedisulfonimide (**1**; 10 mol %; 110 mg, 0.5 mmol) was added to a mixture of 2-(3,4-dimethoxyphenyl)ethanamine (**2a**; 0.91 g, 5 mmol) and benzaldehyde (**3a**; 0.53 g, 5 mmol). The mixture was stirred and heated at 80 °C. The reaction was monitored by GC and GC-MS. First, the complete disappearance of **2a** and **3a**, then the formation of intermediate **4a** and product **5a** were observed (30

min) and finally the total interconversion of **4a** to **5a** (6 hours). Cold water (20 ml) was added to the reaction mixture, which was cooled to 0-5 °C, under vigorous stirring. The resulting solid was filtered on a buchner funnel and washed with additional cold water (5 ml). It was virtually pure (GC, GC-MS, ¹H NMR, ¹³C NMR) title compound **5a**, white solid; yield: 89% (1.61 g). The aqueous washings were collected and evaporated under reduced pressure. After removal of the water, virtually pure (¹H NMR) *o*-benzenedisulfonimide (**1**) was recovered (92 mg, 84% yield). The same procedure was employed in the preparation of tetrahydro-β-carbolines **8**.

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- ^{13}C NMR (50 MHz, CDCl_3): δ = 148.8, 147.4, 131.1, 127.8, 111.6, 109.5, 56.5, 56.1, 55.9, 43.4, 37.0, 32.1, 29.8, 26.1, 25.6.
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